PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/050680	16.02.2005	19.02.2004

International Patent Classification (IPC) or both national classification and IPC
C07D233/28, A61K31/4164

Applicant
SOLVAY PHARMACEUTICALS B.V.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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Authorized Officer

Scruton-Evans, I

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/050680

Box No. I Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 9,1,2,8-12(partly)

because:

☒ the said international application, or the said claims Nos. 9 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1,2,8-12(partly)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	5-7
Industrial applicability (IA)	Yes:	Claims	1-8,10-12
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 9 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).
Claims 1,2,8-12 relate to a compound or use defined by reference to a desirable characteristic or property, namely that it be a prodrug of formula I compounds. The claims cover all compounds having this characteristic, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support and the application so lacks disclosure that a meaningful search over the whole of the claimed scope was impossible. Independent of the above reasoning the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again this lack of clarity in the present case is such as to have rendered a meaningful search over the whole claimed scope impossible. Consequently the search, and this opinion, is limited to those parts which appear to be clear, supported and disclosed, namely the compounds of formula I with the definitions as in claim 1, but not their prodrugs.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents cited in the Search Report are referred to in this communication;

D1: WO 03/026647 A (TIPKER JACOBUS ;HERREMANS ARNOLDUS H J (NL);

KRUSE CORNELIS G (NL)) 3 April 2003 (2003-04-03)

D2: WO 03/027076 A (HERREMANS ARNOLDUS H J ;KRUSE CORNELIS G (NL); LANGE JOSEPHUS H M) 3 April 2003 (2003-04-03)

D3: WO 03/078413 A (MCCREARY ANDREW C ;DIJKSMAN JESSICA A R (NL); HERREMANS ARNOLDUS H) 25 September 2003 (2003-09-25)

D4: LANGE J H M ET AL: 'SYNTHESIS, BIOLOGICAL PROPERTIES, AND MOLECULAR MODELING INVESTIGATIONS OF NOVEL 3,4-DIARYLPYRAZOLINES AS POTENT AND SELECTIVE CB1 CANNABINOID RECEPTOR ANTAGONISTS' JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 47, no. 3, 2004, pages 627-643, XP001188902 ISSN: 0022-2623

D5: KHANNA I K ET AL: 'SELECTIVE CYCLOOXYGENASE-2 INHIBITORS: HETEROARYL MODIFIED 1,2-DIARYLIMIDAZOLES ARE POTENT, ORALLY ACTIVE ANTIINFLAMMATORY AGENTS' JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 43, no. 16, 2000, pages 3168-3185, XP001026112 ISSN: 0022-2623

D6: WO 03/101969 A (UNIV MICHIGAN) 11 December 2003 (2003-12-11)

With regard to the requirement for novelty (Article 33(2) of the PCT), for the claimed subject matter, but only compounds of formula I, their salts and tautomers and stereoisomer, the following assessment is made;

D1 and D4 discloses compounds which differ from formula I in that they are dihydropyrazoles, D2 in that they are imidazoles, D3 in that they are thiazoles and D6 in the nature of the group R2 . For the intermediates of claims 5-7, the equivalent differences apply when appropriate, and re D5, the difference lies in the fact that the substituent on R2 may not be SMe or SO2Me (see definitions of Y in claim 1 and compounds 23,24 from D5).

Article 33(2) of the PCT thus appears to have been satisfied.

With regard to the requirement for inventive step (Article 33(3) of the PCT), for the

end-products (but not the prodrugs thereof - see above), the problem underlying the present application can be seen as the provision of further novel compounds with CB1 receptor activity. The prior arts D1-D4 all disclose compounds with the same qualitative activity. Certain structural characteristics are shared by these prior art compounds, but D2 is considered to represent the closest prior art. The man skilled in the art, faced with the problem as defined above, may have considered the dihydroderivatives of D2 as a possible solution, but it cannot be said with any degree of accuracy that he would have been unambiguously led to these compounds, especially given that imidazolidines of D6 have a different qualitative activity. Thus for those compounds prepared and tested, and a reasonable generalisation thereof, an inventive step could be acknowledged.

For the intermediates of claims 5-7, although they share a structural similarity with the end products, they take part in an analogy process for the preparation of the end products. At least for the compounds of formula IV, the man skilled in the art had available to him in the form of the compounds of D5, compounds which could be equally well be used with minor synthetic modification (in the substituent on the phenyl group), and it is thus considered that they cannot benefit from the inventive step acknowledged for the end products, and the Applicant is asked to demonstrate wherein their inventive step lies (the compounds of formulae V and VI) are analogous to III and II in D2). Article 33(3) of the PCT is thus not satisfied for claims 5-7.

For the assessment of the present claim 9 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII

Certain defects in the international application

Claim 2 should be made dependent on claim 1, and claim 9 should be made more concise by referring back to claim 1.